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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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MARK B WILSON
ARNOLD WHITE & DURKEE
P O BOX 4433
HOUSTON TX 77210-4433

EXAMINER	
SCHWARTZMAN, R	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 08/726,211	Applicant(s) Tormo et al.
	Examiner Robert Schwartzman	Group Art Unit 1636

☒ Responsive to communication(s) filed on *Jan 12, 1998* .

☒ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-20* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-20* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *6, 7, 8*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

— SEE OFFICE ACTION ON THE FOLLOWING PAGES —

DETAILED ACTION

This Office Action is in response to the amendment filed January 12, 1998. Claims 1-20 are pending in this application.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-9 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 1 and 9 have been amended in the preliminary amendment filed August 6, 1997 to include a negative limitation excluding cationic lipids from the polynucleotide/lipid composition. No support for this limitation is found in the present specification. Therefore, this limitation is deemed to be new matter (see 37 CFR 1.118) and must be removed from the claim.

Claims 10-20 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 10-20 are drawn to a method of inhibiting proliferation of a Bcl-2-associated disease cell which expresses both Bcl-2 and Bax comprising administering a polynucleotide which hybridizes to Bcl-2 in association with a lipid. The claims are broadly drawn to any Bcl-2-associated disease in which the diseased cells express Bax. The claims are also broadly drawn to any polynucleotide which hybridizes to Bcl-2. The prior art at the time the present invention was made, as evidenced in the review by Rojanasakul cited in the previous Office Action mailed July 8, 1997, recognized that the effective use of antisense oligonucleotides *in vivo* for disease therapy has been limited due to several problems and that no protocol has been found to routinely achieve a therapeutic benefit with antisense oligonucleotides. This lack of success points to the unpredictability of antisense based therapy. The present specification discloses an *in vitro* example in which the proliferation of Johnson cells is inhibited by administration of a polynucleotide targeted to Bcl-2. No other cells, including others that overexpress Bcl-2, were inhibited. Applicants have further submitted a declaration by Drs. Tari and Lopez-Berestein describing *in vivo* experiments in two mouse models. Johnson cells were injected into nude mice or SCID mice and one week after implantation a liposomal Bcl-2 antisense composition was

administered. Some benefit was achieved by administration of the polynucleotide composition. These examples are not deemed to provide adequate support for the present invention as broadly claimed. The examples utilize Johnson cells only, a follicular lymphoma cell line. No evidence is presented to show that the results obtained using Johnson cells *in vitro* or *in vivo* is correlated with effective treatment of follicular lymphoma cells or any other diseased cell associated with Bcl-2 overexpression. The use of immunocompromised mice in the *in vivo* experiments is completely unpredictive of possible results in normal patients. These experiments also use a particular P-ethoxy oligonucleotide sequence targeted to the translation initiation site of Bcl-2 while the claim is drawn to any polynucleotide. No evidence is provided to show that any other polynucleotide with a different sequence, target site or modification would work in this method. Similarly, the experiments use a liposome composition comprising neutral phospholipids but the claims are drawn to any neutral lipid in any structure. No evidence is provided to show that any lipid composition other than a liposome comprising neutral phospholipids would work in the claimed method. The claims are drawn to treatment of any Bcl-2-associated disease cell which expresses Bax but the specification discloses that the claimed method does not work with cells which overexpress Bcl-2 for reasons other than a t(14;18) translocation, whether or not these cells express Bax (e.g., Raji cells, which overexpress Bcl-2 and express Bax but are not significantly inhibited by the claimed composition). Taken together, these facts indicate that the claims are far broader than what is disclosed by the working examples. Claims 18-20 are drawn to specific conditions for administration of the liposomal oligonucleotide to a human. However,

no evidence is provided to show that the claimed protocol would be effective in inhibiting proliferation of a Bcl-2-associated disease cell. Based on the unpredictability on the area of the invention, the lack of prior art success, the limited working examples and the broadness of the claims, one of skill in the art could not practice the claimed invention without undue experimentation.

Applicants argue that the specification more than adequately describes how to make and use the claimed invention, that the specification teaches to treat cells that overexpress Bcl-2 and that also express Bax and that the methods disclosed in the specification overcome the unpredictability of antisense technology. These arguments have been fully considered but are not deemed to be persuasive. The specification discloses that of the two cell lines tested *in vitro* which overexpress Bcl-2 and also express Bax, Johnson and Raji cells, only one is sensitive to antisense Bcl-2 treatment. As discussed in the specification, the difference in sensitivity may be due to the translocation causing overproduction of Bcl-2 in Johnson cells. However, the claims are drawn to the treatment of any cell overexpressing Bcl-2 and expressing Bax. The specification does not provide guidance as to which cells having these conditions are amenable to the claimed method so the skilled artisan would have to empirically test every cell fitting this description to determine if the method would work. This would be undue experimentation. The specific administration protocols for treating a human with the liposomal antisense composition disclosed in the specification and claimed are not deemed to overcome the inherent

unpredictability of antisense technology as no evidence is provided that the claimed protocol would be effective in humans for the treatment of any Bcl-2-associated disease. No evidence or teaching is provided to show that the administration protocol used in the mouse model experiments is related to or predictive of the administration protocol that is claimed. Thus, given the lack of prior art success in developing an effective administration protocol for antisense oligonucleotides and the lack of evidence for the effectiveness of the disclosed and claimed protocol, the specification is not enabling for how to use the claimed invention.

Applicants further quote the M.P.E.P. to show that *in vitro* assays and/or animal model tests almost invariably will be sufficient to establish therapeutic utility and that the mere fact that something has not previously been done is not, in itself, a sufficient basis for rejecting all applications purporting to disclose how to do it. These arguments have been fully considered but are not deemed to be persuasive. The key part of the quotation from M.P.E.P. 2107.02(c) is that the *in vitro* assays and or animal models must be reasonably correlated to the particular therapeutic utility. As stated above, no evidence of an art-recognized nexus between results obtained with Johnson cells in immunocompromised mice and the effectiveness of treatment of any Bcl-2-associated disease cell which expresses Bax has been provided. Therefore, these experiments do not provide sufficient support for the claimed method. Furthermore, it should be noted that the utility of the claimed invention is not part of the rejection of record. Utility is a rejection under 35 U.S.C. 101. Further, the guidelines as published, Federal Register (60 FR

36263, July 14, 1995), clearly state that a rejection under 35 U.S.C. 112 "how to use" is entirely proper absent a rejection under 35 U.S.C. 101. The rejection of record is under 35 U.S.C. 112, "how to use". While the artisan may consider the invention credible, this is not the same as having an enabling disclosure at the time of filing. A utility for the claimed invention can be considered credible, and thus 101 is satisfied, while the specification does not teach how to use the claimed invention. The basic argument, reiterated here, is that the specification does not provide sufficient guidance to the skilled artisan for a method of inhibiting the proliferation of any Bcl-2-associated disease cell using any polynucleotide which hybridizes to Bcl-2. Regarding the quotation from the M.P.E.P. that the fact that something has not previously been done is not, by itself, sufficient for rejecting an application, the present rejection is not based solely on the fact that treatment of Bcl-2-associated diseases with antisense Bcl-2 has not previously been done. This rejection is based on the multiple factors discussed in *In re Wands*, 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988). The claimed invention is deemed to be not enabled based on the a combination of the breadth of the claims, the unpredictable nature of antisense technology, the state of the prior art, the absence of reasonably correlated working examples, the amount of direction or guidance provided and the quantity of experimentation necessary. It is this combination of factors which provides sufficient reason to doubt that the specification is adequate to teach how to make and use the invention.

Applicants further argue that the declaration of Drs. Tari and Lopez-Berestein describing mouse model data shows the correlation between the described *in vitro* activity and the asserted

utility of the liposomal antisense composition. This argument has been fully considered but is not deemed to be persuasive for the reasons stated above. No evidence of a correlation between the results obtained in an animal model of injected tumor cell lines in immunocompromised mice and tumors in a human is provided. Furthermore, the evidence provided in the declaration using Johnson cells and a single liposomal composition containing one specific antisense sequence cannot provide support for the broadly written claims.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 10-20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 10 is vague and indefinite as it does not provide a positive process step which clearly relates back to the preamble.

Claim Rejections - 35 USC § 102

The rejection of claims 1-6 and 9 under 35 U.S.C. 102(b) as being anticipated by Evan is withdrawn in view of the amendments to the claims.

The rejection of claims 1-6 under 35 U.S.C. 102(b) as being anticipated by Reed is withdrawn in view of the amendments to the claims.

The rejection of claims 1 and 2 under 35 U.S.C. 102(a) as being anticipated by Almazan et al. is withdrawn in view of the declaration filed under 37 C.F.R. 1.131.

The rejection of claims 1, 2, 5 and 6 under 35 U.S.C. 102(a) as being anticipated by Tormo et al. is withdrawn in view of the declaration filed under 37 C.F.R. 1.131.

The rejection of claims 1-6 and 9 under 35 U.S.C. 102(e) as being anticipated by Green et al. is withdrawn in view of the amendments to the claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The rejection of claims 7 and 8 under 35 U.S.C. 103(a) as being unpatentable over Evan or Reed or Tormo et al. or Green et al. in view of Ledley is withdrawn in view of the amendments to the claims.

Claims 1-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Evan or Reed or Green et al. each in view of Tari et al.

Evan teaches the use of an antisense oligonucleotide targeted to Bcl-2 to prevent expression of the Bcl-2 protein (page 7, lines 10-29). The oligonucleotide is preferably targeted to the translation initiation site of Bcl-2 and preferably comprises the sequence of claimed SEQ ID NO: 1 (page 15, lines 16-23). The antisense oligonucleotide can be synthesized from an expression construct encoding the oligonucleotide (page 18, lines 26-30). The antisense

oligonucleotide or expression construct is preferably delivered into cells as composition comprising a liposome (page 59, lines 6-7).

Reed teaches the use of an antisense oligonucleotide targeted to Bcl-2 to prevent expression of the Bcl-2 protein (page 3, lines 2-22). The oligonucleotide is preferably targeted to the translation initiation site of Bcl-2 and preferably comprises the sequence of claimed SEQ ID NO: 1 (page 13, lines 2-5). The antisense oligonucleotide or expression construct is preferably delivered into cells as composition comprising a liposome (page 14, lines 16-25).

Green et al. teaches antisense oligonucleotides targeted to anti-apoptotic genes such as Bcl-2 (column 3, lines 51-67). The oligonucleotide is preferably targeted to a region including the translation start site of the anti-apoptotic gene (column 4, lines 46-51). The antisense oligonucleotide can be encapsulated into liposomes for administration (column 6, lines 60-63). Expression vectors that express the antisense oligonucleotide in a cell are disclosed (column 6, lines 8-10).

None of these references teach a liposome made of neutral lipids, phosphatidylcholine, phosphatidylglycerol, phosphatidylethanolamine or dioleoylphosphatidylcholine. Tari et al. teaches a composition comprising an antisense oligonucleotide encapsulated in a liposome (column 1, line 66-column 2, line 56). The liposome is made from a phospholipid selected from a

phosphatidylcholine or a phosphatidylserine, preferably dioleoylphosphatidylcholine (column 2, lines 10-14). It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to make a composition comprising an antisense oligonucleotide targeted to Bcl-2 encapsulated in a liposome as taught by Evan or Reed or Green et al. and to use the liposomal formulations taught by Tari et al., motivated by the teaching of Tari et al. that liposomes comprising dioleoylphosphatidylcholine impart improved stability and cellular uptake to the antisense oligonucleotides.

Conclusion

Claims 1-20 remain rejected.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period

will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert Schwartzman whose telephone number is (703) 308-7307. The examiner can normally be reached on Monday through Friday from 6:30 AM to 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, George Elliott, can be reached at (703) 308-4003. The fax number for this group is (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703)-308-0196.

NANCY DEGEN
PRIMARY EXAMINER

Robert A. Schwartzman, Ph.D.
March 5, 1998